

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Berka *et al.*

Confirmation No. 6980

Serial No.: 09/533,559

Group Art Unit: 1631

Filed: March 22, 2000

Examiner: J.S. Brusca

For: Methods For Monitoring Multiple Gene Expression

**DECLARATION UNDER 37 C.F.R. § 1.132**

Commissioner for Patents  
Washington, DC 20231

Sir:

I, Randy Berka, do hereby state and declare that

1. I am one of the inventors of the subject matter disclosed and claimed in the above-captioned application.
2. I received a Ph.D. in Microbiology and Immunology from the University of Colorado, Health Science Center, Denver, Colorado, in 1983. I have been employed at Novozymes Biotech, Inc., Davis, California, since 1992 where I am currently a Research Fellow.
3. I have read the Office Action dated November 7, 2002 and the Advisory Action dated May 22, 2003 issued in connection with the above-referenced patent application and understand that claims 103-110 have been rejected under 35 U.S.C. § 101 as not supported by a substantial utility. I respectfully disagree with this conclusion.
4. Using Applicants' disclosure in the above-captioned application, one of ordinary skill in the art would be able to set-up and use the methods of the present invention to monitor global expression of a plurality of genes from a filamentous fungal cell with respect to a particular phenotype such as improved secretion or production of a protein or compound, reduced or no secretion or production of a protein or compound, improved or reduced expression of a gene or pathway, desirable morphology, an altered growth rate under desired conditions, relief of over-expression mediated growth inhibition, or tolerance to low oxygen conditions; to discover new genes; to identify possible functions of unknown open reading frames; and to monitor gene copy number variation and stability. For example, the global view of changes in expression of genes may be used to provide a picture of the way in which filamentous fungal cells adapt to changes in culture conditions, environmental stress, or other physiological provocation. Applicants also

provide other possibilities for monitoring global expression including spore formation/germination, recombination, metabolic or catabolic pathway engineering.

5. The experimental study and results described below demonstrate that claims 103-110 are supported by a substantial utility. The study was performed using the protocols described in the above-captioned application.

6. A recombinant *Aspergillus oryzae* strain containing a *Thermomyces lanuginosus* lipase gene (Le-1) and a yield- and morphologically improved mutant (7-1) of Le-1 were analyzed using microarrays containing the *Aspergillus oryzae* ESTs disclosed in the above-captioned application. When Le-1 is grown in laboratory fermentors it displays a very pronounced "ballooning" phenotype where the mycelium becomes bloated and fragmented. After approximately 90 hours of fermentation the culture undergoes a significant morphological change and becomes more viscous. Concomitantly the dissolved air tension drops rapidly and production of the lipase ceases. Mutant 7-1 was isolated as a classical mutant of Le-1 by mutagenesis and high-throughput screening. This mutant displays a much lower degree of ballooning and does not display the catastrophic changes in fermentation morphology and productivity. The initial productivity of 7-1 is similar to that of Le-1, but, in contrast to Le-1, does not stop producing lipase after 90 hours.

7. Samples of mRNA extracted from strains Le-1 and 7-1 cultivated in 1 L fermentors for 3 or 4 days were labeled and hybridized to a microarray containing the *Aspergillus oryzae* ESTs described in Appendix A. Each strain was fermented twice yielding a total of 4 samples per strain for microarray analysis. In each hybridization mRNAs from Le-1 and 7-1 were labeled with different fluorophores, mixed, and hybridized to the slide. Samples from Le-1 (day 3) were compared to samples from 7-1 (day 3), and samples from the two strains at four days post inoculum were also compared. A total of 5 hybridizations were performed with mRNA extracted from day 3 samples, and 2 hybridizations were performed with mRNA extracted from day 4 samples. The samples from each strain at day 4 were from the same fermentation and thus represent technical replicates rather than biological replicates. Microarray slides from the hybridizations were scanned and the image data analyzed as described in the above-captioned application. The data from each time point were used as replicates for the identification of significantly differentially regulated genes on a 95% confidence level. This yielded a list of differentially regulated genes from each time point (shown in Appendix A).

8. Analysis revealed a number of genes whose transcript levels differed between the strains. Among these genes were 53 ribosomal genes and 27 genes identified as being involved in cell wall synthesis and morphogenesis, indicating that general protein production and the cell wall metabolism is regulated differently in the strains. These results fit well with the observation that the morphology of the two strains is different, especially with regard to the degree of "ballooning" when expressing the lipase gene.

9. From the list in Appendix A, it is obvious that the ribosomal genes are differentially expressed between the two strains. The 53 ribosomal genes are consistently down-regulated in 7-1 compared to Le-1 on both day 3 and day 4. Similarly, three genes with homology to the translation initiation factor 3 from *Schizosaccharomyces pombe* are down-regulated in 7-1 while 5 of 6 genes with homology to tRNAs are up-regulated in 7-1. The consistent down-regulation of genes involved in translation indicates that 7-1 has generally reduced translational activity compared to Le-1, which may relieve some of the secretional stress and reduce the degree of ballooning seen in Le-1. It may also reduce the counter-selective pressure against lipase-producing cells that may be responsible for the rapid loss of expression potential in Le-1

cultures after 90 hours of fermentation, allowing 7-1 to retain its expression potential throughout the fermentation. Another explanation could be that the growth rate of the 7-1 cells are lower than that of Le-1. The cultures are dosed approximately the same amount of glucose during fermentation, but the Le-1 culture changes composition rather abruptly in the period leading up to the 90 hours time point. The Le-1 cells that produce lipase become inactive and ultimately die while the culture is taken over by cells that have lost lipase production capacity.

10. The list of differentially regulated genes in Appendix A shows 27 genes involved in cell-wall synthesis. Twenty of these genes are consistently up-regulated while seven are down-regulated in 7-1 compared to Le-1. Figure 1 shows a model for the synthesis of  $\beta$ -glucans in the cell wall of fungi. Some of the genes listed in Appendix A can be assigned (by homology to genes of known or putative function) to the first three steps of cell wall synthesis as depicted in Figure 1. Among the genes that can be assigned to the first step, biosynthesis of linear 1,3- $\beta$ -glucans, is a homolog of FSK (*Aspergillus fumigatus*, Kelly et al. 1996, *J. Bact.* 178: 4381-4391; Beauvais et al. 2001, *J. Bact.* 183: 2273-2279), RHO2 (regulator of  $\alpha$ -glucan biosynthesis in *S. pombe*, Hirata et al. 1998, *J. Cell Sci.* 111: 149-159), RHO-GTPase (same family of proteins as RHO2), and RHO GDP dissociation inhibitor (Sasaki & Takai, 1998, *J. Bact.* 183: 2273-2279). FSK and RHO2 are up-regulated while the RHO GDP dissociation inhibitor is down-regulated. The results suggest that the  $\beta$ -glucan synthesis pathway is up-regulated.

11. Two of the differentially regulated genes in Appendix A can be assigned to the second step in the biosynthesis of  $\beta$ -glucan, namely a protein with homology to a *Fusarium venenatum* glucanase and a protein with homology to an *Aspergillus fumigatus*  $\beta$ -1,3-glucanosyltransferase. Both proteins have homology to the Bgl2 protein from *Saccharomyces cerevisiae*. The *Aspergillus fumigatus* homolog have been shown to introduce intrachain 1,6- $\beta$ -linkages into 1,3- $\beta$ -glucan, although the role of the *Aspergillus fumigatus* protein in cell wall synthesis is yet unclear (Mouyna et al., 1998, *Microbiology* 144: 3171-3180).

12. Five genes from Appendix A can be assigned to the third step in the pathway shown in Figure 1. Each of these genes has homology to one of the three GEL genes identified in *Aspergillus fumigatus* (Mouyna et al., 2000, *J. Biol. Chem.* 275: 14882-14889; Mouyna et al., 2000, *Biochem. J.* 347: 741-747). The GEL1p protein is the most intensively studied enzyme of the three and encodes a glycosylphosphatidylinositol-anchored  $\beta$ -1,3-glucanosyltransferase that cleaves a  $\beta$ -1,3-glucan internally and transfers the reducing end to the non-reducing end of another  $\beta$ -1,3-glucan molecule, resulting in elongation of this glucan chain. While deletion of the GEL1p protein does not confer a phenotype to *Aspergillus fumigatus*, a GEL2p mutant has a reduced growth rate and altered conidiation. The GEL3p protein is not expressed in standard culture conditions (Bernard and Latgé, 2001, *Med. Mycol.* 39, suppl. 1, 9-17). In strain 7-1 the GEL1p and GEL2p homologues are up-regulated, but the GEL3p homologues are down-regulated. The regulation patterns of the differentially expressed genes involved in cell-wall synthesis suggest that the  $\beta$ -glucan synthesis pathway is up-regulated in strain 7-1 compared to Le-1. The physiological effect of the increased activity of this pathway is consistent with the reduced ballooning seen in 7-1, since it may be that the ballooning phenotype could be caused by a deficiency of cell-wall components at the hyphae elongation sites, and that this deficiency could be an effect of immense overloading of the secretion machinery in the cells. While the up-regulation of proteins that take part in cell-wall synthesis *in situ* does not reduce the pressure on the secretion pathway, it may increase the secretion of cell-wall synthesis enzymes at the expense of other, less crucial, enzymes.

12. The results described above clearly demonstrate that the microarrays produced from the

*Aspergillus oryzae* ESTs provide a powerful tool to study the effect of strain differences on global gene expression in the cells. Especially in the context of mutants produced by "classical" means (i.e., by radiation or chemical mutagenesis) the microarray analysis provides one of the very few methods for identifying the genetic targets of the mutagens. Without this technique it would be an almost impossible task to identify the pathways and ideally the genes that are affected by the introduced mutations.

13. The undersigned declarant declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize any patent issuing thereon.

Signed this 16 day of September 2003

  
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Randy Berka

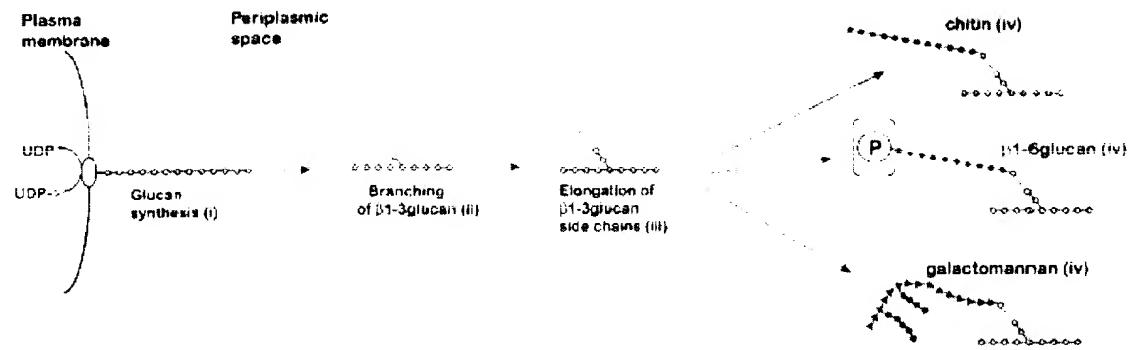


Figure 1. Chronological events involved in the synthesis and postsynthetic modifications of the cell wall 1,3- $\beta$ -glucans. (i) Biosynthesis of linear 1,3- $\beta$ -glucan; (ii) branching of 1,3- $\beta$ -glucans through 1,6- $\beta$ -glucan side chains; (iii) elongation of 1,3- $\beta$ -glucan side chains; and (iv) cross-linking of other polymers (chitin and galactomannan in *A. fumigatus*, or chitin, 1,6- $\beta$ -glucan, and proteins in *S. cerevisiae*) onto non-reducing ends of 1,3- $\beta$ -glucan side chains. *P*, proteins. From Mouyna *et al.* 2000a.

## Appendix A

Differentially expressed genes in 7-1 compared to Le-1 on day 3 and day 4.

| Annotation  | Pathway       | Fold reg. day 3 | Fold reg. day 4 |
|---|---------------|-----------------|-----------------|
| TREMBL:Q9P380 Schizosaccharomyces pombe PUTATIVE PEPTIDE TRANSPORTER.   | AA-transport  | 2,8             | 2,6             |
| SWISSPROT:P19145 Saccharomyces cerevisiae General amino-acid permease GAP1.   | AA-transport  | 2,6             | 3,4             |
| SWISSPROT:P53388 Saccharomyces cerevisiae Dicarboxylic amino acid permease.   | AA-transport  | 2,5             | 3,1             |
| SWISSPROT:P53090 Saccharomyces cerevisiae Aromatic amino acid aminotransferase I (EC 2.6.1.-).                        | AA-transport  | 1,4             | 2,1             |
| SWISSPROT:P38090 Saccharomyces cerevisiae General amino acid permease AGP2.   | AA-transport  | 1,3             | 1,8             |
| TREMBL:Q96W94 Saccharomyces kluveri (EC=3.5.1.6) BETA-ALANINE SYNTHASE (EC 3.5.1.6).                                  | AA-metabolism | 3,6             | 2,2             |
| SWISSPROT:Q92413 Emericella nidulans (EC=2.6.1.13) Ornithine aminotransferase (EC 2.6.1.13) (Ornithine-oxo-aci        | AA-metabolism | 2,1             | 3,1             |
| TREMBL:Q96V52 Emericella nidulans (EC=6.3.1.2) GLUTAMINE SYNTHETASE (EC 6.3.1.2)                                      | AA-metabolism | 1,9             | 2,4             |
| TREMBL:Q93H39 Streptomyces avermitilis NCN-RIBOSOMAL PEPTIDE SYNTHETASE.  | AA-metabolism | 1,7             | 1,2             |
| TREMBL:Q9Y7G4 Emericella nidulans CARNITINE/ACYL CARNITINE CARRIER.   | AA-metabolism | 1,6             | 1,5             |
| TREMBL:Q9P8T7 Paracoccidioides brasiliensis ORNITHINE DECARBOXYLASE.  | AA-metabolism | 1,5             | 1,3             |
| SWISSPROT:Q12611 Emericella nidulans (EC=3.5.3.1) Arginase (EC 3.5.3.1)   | AA-metabolism | 1,4             | 1,5             |
| TREMBL:Q9Y7B2 Emericella nidulans (EC=5.4.99.5) CHORISMATE MUTASE (EC 5.4.99.5).                                      | AA-metabolism | 1,4             | 1,4             |
| SWISSPROT:O74787 Schizosaccharomyces pombe (EC=2.1.1.17) Phosphatidylethanolamine N-methyltransferase (EC 2.1.1.17)   | AA-metabolism | 1,4             | 1,4             |
| TREMBL:O42652 Schizosaccharomyces pombe (EC=2.6.1.1) PUTATIVE ASPARTATE AMINOTRANSFERASE, CYTOPLASMIC (EC 2.6.1.1)    | AA-metabolism | -1,3            | -3,1            |
| SWISSPROT:P17324 Saccharomyces cerevisiae (EC=4.2.1.13) L-serine dehydratase (EC 4.2.1.13) (L-serine deaminase).      | AA-metabolism | -1,5            | -10,7           |
| TREMBL:Q9HFU6 Emericella nidulans ORNITHINE DECARBOXYLASE ANTIZYME.   | AA-metabolism | -1,6            | -2,1            |
| TREMBL:Q96WX7 Emericella nidulans (EC=1.5.1.2) PUTATIVE PYRROLINE-5-CARBOXYLATE REDUCTASE (EC 1.5.1.2).               | AA-metabolism | -1,7            | -1,6            |
| TREMBL:Q9P444 Emericella nidulans (EC=2.1.1.14) COBALAMIN-INDEPENDENT METHIONINE SYNTHASE (EC 2.1.1.14).              | AA-metabolism | -1,8            | -1,8            |
| TREMBL:Q9Y7N4 Schizosaccharomyces pombe (EC=1.4.3.3) PUTATIVE D-AMINO ACID OXIDASE (EC 1.4.3.3) (DAMOX) (DAO)         | AA-metabolism | -1,9            | -1,3            |
| TREMBL:Q8X019 Neurospora crassa KETOL-ACID REDUCTOISOMERASE (ILV-2).  | AA-metabolism | -2,4            | -1,9            |
| SWISSPROT:P38088 Saccharomyces cerevisiae (EC=6.1.1.14) Glycyl-tRNA synthetase (EC 6.1.1.14) (Glycine-tRNA ligase)    | tRNA          | 1,9             | 1,4             |
| SWISSPROT:P09880 Saccharomyces cerevisiae (EC=6.5.1.3) tRNA ligase (EC 6.5.1.3).                                      | tRNA          | 1,7             | 1,4             |
| SWISSPROT:O42870 Schizosaccharomyces pombe (EC=6.1.1.20) Phenylalanyl-tRNA synthetase alpha chain (EC 6.1.1.20) (Phen | tRNA          | 1,5             | 1,4             |
| TREMBL:CAD37006 Neurospora crassa Probable tma splicing protein sp1.  | tRNA          | 1,5             | 1,5             |
| TREMBL:O74781 Schizosaccharomyces pombe (EC=6.1.1.19) PUTATIVE ARGINYL-TRNA SYNTHETASE, CYTOPLASMIC (EC 6.1.1.19).    | tRNA          | 1,4             | 1,6             |
| SWISSPROT:P04802 Saccharomyces cerevisiae (EC=6.1.1.12) Aspartyl-tRNA synthetase, cytoplasmic (EC 6.1.1.12) (Asparta  | tRNA          | -1,5            | -1,2            |
| SWISSPROT:Q12207 Saccharomyces cerevisiae Non-classical export protein 2.   | Transport     | -3,6            | -4,4            |
| SWISSPROT:O14164 Schizosaccharomyces pombe Probable eukaryotic translation initiation factor 3 93 kDa s               | translation   | -1,3            | -1,3            |
| SWISSPROT:O59742 Schizosaccharomyces pombe Probable eukaryotic translation initiation factor 3 135 kDa                | translation   | -1,6            | -1,8            |
| SWISSPROT:O59742 Schizosaccharomyces pombe Probable eukaryotic translation initiation factor 3 135 kDa                | translation   | -2,2            | -1,4            |
| SWISSPROT:Q9UST4 Schizosaccharomyces pombe Initiation factor 5A-2 (eIF-5A 2).   | Transcription | 2,3             | 1,4             |
| TREMBL:Q9P3D9 Neurospora crassa RELATED TO GTP-BINDING PROTEIN RAB2.  | Transcription | 2,3             | 2,0             |
| SWISSPROT:Q12753 Saccharomyces cerevisiae Transcriptional activator HAA1.   | Transcription | 1,7             | 1,2             |
| TREMBL:Q9HEX7 Pneumocystis carinii HELIX-LOOP-HELIX DNA BINDING PROTEIN   | Transcription | 1,5             | 1,4             |
| TREMBL:AAM22470 Fusarium solani Cutinase transcription factor 1 alpha   | Transcription | 1,4             | 1,3             |
| SWISSPROT:Q12731 Emericella nidulans Transcription initiation factor TFIID (TATA-box factor) (TAT                     | Transcription | 1,3             | 1,6             |
| SWISSPROT:P08153 Saccharomyces cerevisiae Transcriptional factor SWI5.  | Transcription | 1,3             | 2,4             |
| TREMBL:O59849 Aspergillus oryzae HAPE.  | Transcription | 1,3             | 1,5             |
| TREMBL:Q00069 Ascobolus immersus ZINC FINGER PROTEIN.   | Transcription | -1,2            | -2,4            |
| SWISSPROT:P49373 Schizosaccharomyces pombe Transcription elongation factor S-II (TFIIS).                              | Transcription | -1,3            | -1,3            |
| SWISSPROT:Q92371 Schizosaccharomyces pombe Transcription factor BTF3 homolog.   | Transcription | -1,4            | -1,3            |
| SWISSPROT:P47943 Schizosaccharomyces pombe Eukaryotic initiation factor 4A (eIF-4A) (eIF4A).                          | Transcription | -2,1            | -1,4            |
| SWISSPROT:Q92794 Homo sapiens Monocytic leukemia zinc finger protein (Zinc finger protein                             | Transcription | -2,2            | -5,5            |

| Annotation  | Pathway          | Fold reg.<br>day 3 | Fold reg.<br>day 4 |
|---|------------------|--------------------|--------------------|
| GENESEQP:AAE06000 Unidentified Zinc finger protein (ZFP) m1 protein.  | Transcription    | -2,6               | -23,0              |
| TREMBL:Q96WT5 Aspergillus oryzae MALTOSE PERMEASE.  | sugar-transport  | 3,6                | 6,3                |
| ERDBP:NP000895 Fusarium oxysporum F. oxysporum Glucose Transporter  | sugar-transport  | 1,9                | 9,5                |
| SWISSPROT:P15325 <i>Emeucella nidulans</i> Quinate permease (Quinate transporter).  | sugar-transport  | 1,8                | 1,5                |
| TREMBL:Q9P3B9 <i>Neurospora crassa</i> RELATED TO MYO-INSITOL TRANSPORT PROTEIN ITR1.   | sugar-transport  | -1,2               | -1,9               |
| SWISSPROT:Q92253 <i>Neurospora crassa</i> Probable glucose transporter rco-3.   | sugar-transport  | -2,0               | -3,9               |
| SWISSPROT:Q92253 <i>Neurospora crassa</i> Probable glucose transporter rco-3.   | sugar-transport  | -6,2               | -5,1               |
| SWISSPROT:Q9US15 <i>Schizosaccharomyces pombe</i> Heat shock protein st1 homolog.   | Stress           | 1,8                | 2,4                |
| SWISSPROT:P23724 <i>Saccharomyces cerevisiae</i> (EC=3.4.25.1) Potential proteasome component C5 (EC 3.4.25.1) (Multicatalytic) | Stress           | 1,6                | 1,6                |
| TREMBL:Q8X041 <i>Neurospora crassa</i> RELATED TO HSP90 ASSOCIATED CO-CHAPERONE.  | Stress           | 1,6                | 2,4                |
| TREMBL:Q9HG78 <i>Coccidioides immitis</i> UBIQUITIN CARBOXYL-TERMINAL HYDROLASE (FRAGMENT)                                      | stress           | 1,4                | 2,3                |
| SWISSPROT:Q74225 <i>Neurospora crassa</i> Heat shock protein Hsp88.   | stress           | 1,3                | 1,7                |
| TREMBL:Q9P5S4 <i>Neurospora crassa</i> RELATED TO HSP70 PROTEIN   | stress           | 1,3                | 2,6                |
| SWISSPROT:Q74225 <i>Neurospora crassa</i> Heat shock protein Hsp88.   | stress           | -1,4               | -1,5               |
| GENESEQP:AAR43654 <i>Aspergillus nidulans</i> c424 gene product.  | Stress           | -2,3               | -3,7               |
| GENESEQP:AAR43654 <i>Aspergillus nidulans</i> c424 gene product.  | Stress           | -2,9               | -2,8               |
| SWISSPROT:P18899 <i>Saccharomyces cerevisiae</i> DDR48 stress protein (DNA damage-responsive protein 48) (DDR)                  | Stress           | -3,0               | -3,5               |
| TREMBL:Q9HG46 <i>Aspergillus oryzae</i> PUTATIVE 3-KETOACYL-COA THIOLASE.   | Sterol/Lipid met | 1,4                | 1,2                |
| TREMBL:Q29517 <i>Oryctolagus cuniculus</i> (EC=3.1.4.11) PHOSPHOLIPASE C (EC 3.1.4.11) (FRAGMENT)                               | Sterol/Lipid met | -1,2               | -2,1               |
| GENESEQP:AAB19184 <i>Saccharomyces cerevisiae</i> Lipid metabolism protein encoded by the open reading frame Y                  | Sterol/Lipid met | -1,4               | -1,3               |
| SWISSPROT:O59933 <i>Candida albicans</i> C-4 methyl sterol oxidase (EC 1 ---)   | Sterol/Lipid met | -1,6               | -6,2               |
| SWISSPROT:O14340 <i>Schizosaccharomyces pombe</i> Oxysterol-binding protein homolog C2F12.05c.                                  | Sterol/Lipid met | -1,8               | -3,2               |
| TREMBL:Q9P8R0 <i>Aspergillus fumigatus</i> CYTOCHROME P450 STEROL 14 ALPHA-DEMETHYLASE (14-ALPHA STEROL)                        | Sterol/Lipid met | -2,3               | -45,4              |
| TREMBL:Q9P3J7 <i>Neurospora crassa</i> RELATED TO SPORE COAT PROTEIN SP96.  | Sporulering      | -1,4               | -1,2               |
| TREMBL:Q9P3J7 <i>Neurospora crassa</i> RELATED TO SPORE COAT PROTEIN SP96   | Sporulering      | -2,2               | -1,9               |
| TREMBL:Q96UP0 <i>Neurospora crassa</i> PHEROMONE PPG-1-LIKE PROTEIN (PHEROMONE PRECURSOR).                                      | signalling       | 4,1                | 20,3               |
| TREMBL:Q9GYW6 <i>Drosophila melanogaster</i> THYROID HORMONE RECEPTOR-ASSOCIATED PROTEIN TRAP170 (FRAGMEN                       | signalling       | 1,6                | 1,5                |
| TREMBL:Q74749 <i>Schizosaccharomyces pombe</i> SIMILARITY TO MAMMALIAN SIGNAL TRANSDUCING ADAPTOR                               | signalling       | -1,9               | -2,6               |
| TREMBL:Q9JLE9 <i>Rattus norvegicus</i> GABA-A RECEPTOR EPSILON-LIKE SUBUNIT.  | signalling       | -2,8               | -35,8              |
| SWISSPROT:Q04491 <i>Saccharomyces cerevisiae</i> Protein transport protein SEC13.   | secretion        | 1,7                | 1,9                |
| ERDBP:NP000597 <i>Fusarium venenatum</i> F. venenatum GDI homolog   | secretion        | 1,4                | 1,6                |
| TREMBL:Q8X0K7 <i>Neurospora crassa</i> RELATED TO SECRETORY PROTEIN SSP120.   | secretion        | -1,3               | -3,1               |
| SWISSPROT:P53619 <i>Bos taurus</i> Coatomer delta subunit (Delta-coat protein) (Delta-COP).                                     | secretion        | -1,6               | -1,5               |
| TREMBL:Q8X079 <i>Neurospora crassa</i> RELATED TO RNA HELICASE/RNASEIII CAF.  | RNA              | 1,7                | 1,3                |
| TREMBL:Q00870 <i>Trypanosoma brucei</i> RIBONUCLEASE H1.  | RNA              | 1,6                | 1,2                |
| TREMBL:Q9CWZ3 <i>Mus musculus</i> 2310057C03RIK PROTEIN (RNA BINDING MOTIF PROTEIN 8A)  | RNA              | 1,3                | 2,1                |
| SWISSPROT:Q07478 <i>Saccharomyces cerevisiae</i> Probable ATP-dependent RNA helicase SUB2.                                      | RNA              | 1,3                | 1,7                |
| TREMBL:Q9Y7A8 <i>Neurospora crassa</i> PAD-1.   | RNA              | 1,3                | 1,9                |
| TREMBL:Q9P3U1 <i>Schizosaccharomyces pombe</i> PROTEIN WITH 3 RNA BINDING DOMAINS, YEAST HRB1 HOMOLOGUE.                        | RNA              | -1,3               | -1,4               |
| TREMBL:Q9P3E1 <i>Neurospora crassa</i> RELATED TO RNA-BINDING PROTEIN FUS/TLS.  | RNA              | -1,3               | -1,7               |
| TREMBL:Q9UQ35 <i>Homo sapiens</i> RNA BINDING PROTEIN   | RNA              | -1,8               | -1,3               |
| SWISSPROT:Q74330 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S27   | Ribosomal        | -1,2               | -1,6               |
| SWISSPROT:P53163 <i>Saccharomyces cerevisiae</i> Putative 60S ribosomal protein L7/L12 homolog, mitochondrial                   | Ribosomal        | -1,2               | -1,7               |
| SWISSPROT:P23369 <i>Saccharomyces cerevisiae</i> Mitochondrial 60S ribosomal protein L25 (Yml25)                                | Ribosomal        | -1,3               | -1,4               |
| SWISSPROT:Q10157 <i>Schizosaccharomyces pombe</i> 60S ribosomal protein L11.  | Ribosomal        | -1,4               | -1,4               |
| SWISSPROT:Q42952 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S30.  | Ribosomal        | -1,4               | -1,4               |
| SWISSPROT:P49631 <i>Saccharomyces cerevisiae</i> 60S ribosomal protein L43 (L37A) (Yl35)  | Ribosomal        | -1,4               | -1,7               |
| SWISSPROT:Q9P3T6 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S5-B.   | Ribosomal        | -1,4               | -1,5               |
| SWISSPROT:Q74836 <i>Schizosaccharomyces pombe</i> 60S ribosomal protein L1-B (L10a).  | Ribosomal        | -1,5               | -2,6               |

| Annotation   | Pathway    | Fold reg.<br>day 3 | Fold reg.<br>day 4 |
|--|------------|--------------------|--------------------|
| SWISSPROT:Q9C0T1 <i>Emericella nidulans</i> 60S ribosomal protein L37.                                   | Ribosomal  | -1,5               | -1,3               |
| SWISSPROT:O60128 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S3.                              | Ribosomal  | -1,5               | -1,6               |
| SWISSPROT:O74172 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S25-B (S31-B).                   | Ribosomal  | -1,5               | -2,0               |
| SWISSPROT:O59953 <i>Neurospora crassa</i> 60S ribosomal protein L5 (CPR4).                               | Ribosomal  | -1,6               | -1,4               |
| SWISSPROT:P34737 <i>Podospora anserina</i> 40S ribosomal protein S15 (S12).                              | Ribosomal  | -1,6               | -1,5               |
| SWISSPROT:Q9HFR7 <i>Trichoderma hamatum</i> 60S ribosomal protein L36 (TRP36).                           | Ribosomal  | -1,6               | -1,3               |
| SWISSPROT:P78987 <i>Erysiphe graminis</i> 60S ribosomal protein L27A (L29).                              | Ribosomal  | -1,6               | -1,5               |
| SWISSPROT:P26781 <i>Saccharomyces cerevisiae</i> 40S ribosomal protein S11 (S18) (YS12) (RP41).          | Ribosomal  | -1,7               | -1,7               |
| SWISSPROT:O13672 <i>Schizosaccharomyces pombe</i> 60S ribosomal protein L8 (L7A) (L4).                   | Ribosomal  | -1,7               | -1,7               |
| TREMBL:Q9P4Z0 <i>Neurospora crassa</i> PROBABLE RIBOSOMAL PROTEIN RPS8BP                                 | Ribosomal  | -1,7               | -1,3               |
| SWISSPROT:Q9HE25 <i>Neurospora crassa</i> 60S ribosomal protein L17.                                     | Ribosomal  | -1,7               | -1,8               |
| SWISSPROT:Q9USX4 <i>Schizosaccharomyces pombe</i> 60S ribosomal protein L33-A (L37A).                    | Ribosomal  | -1,7               | -1,6               |
| SWISSPROT:P21772 <i>Neurospora crassa</i> 40S ribosomal protein S26E (CRP5) (13.6 kDa ribosomal protein) | Ribosomal  | -1,8               | -1,4               |
| TREMBL:Q9C2B9 <i>Neurospora crassa</i> PROBABLE RIBOSOMAL PROTEIN L38.                                   | Ribosomal  | -1,8               | -1,9               |
| SWISSPROT:P04451 <i>Saccharomyces cerevisiae</i> 60S ribosomal protein L23 (L17).                        | Ribosomal  | -1,8               | -1,3               |
| SWISSPROT:O13418 <i>Aspergillus niger</i> 60S ribosomal protein L15.                                     | Ribosomal  | -1,8               | -1,8               |
| TREMBL:Q9C2H7 <i>Neurospora crassa</i> PROBABLE RIBOSOMAL PROTEIN RPL4A.                                 | Ribosomal  | -1,8               | -1,5               |
| SWISSPROT:P21772 <i>Neurospora crassa</i> 40S ribosomal protein S26E (CRP5) (13.6 kDa ribosomal protein) | Ribosomal  | -1,9               | -1,5               |
| SWISSPROT:P79015 <i>Schizosaccharomyces pombe</i> 60S ribosomal protein L32-A.                           | Ribosomal  | -1,9               | -2,0               |
| SWISSPROT:Q9P7B2 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S8-B.                            | Ribosomal  | -1,9               | -1,7               |
| TREMBL:Q9HG0 Aspergillus fumigatus ACIDIC RIBOSOMAL PROTEIN P1.  | Ribosomal  | -2,0               | -1,4               |
| TREMBL:Q96W54 <i>Candida albicans</i> RIBOSOMAL PROTEIN S22.   | Ribosomal  | -2,0               | -1,8               |
| SWISSPROT:P05736 <i>Saccharomyces cerevisiae</i> 60S ribosomal protein L2 (YL6) (L5) (RP8).              | Ribosomal  | -2,1               | -1,2               |
| TREMBL:Q9USW5 <i>Schizosaccharomyces pombe</i> 40S RIBOSOMAL PROTEIN S4-2.                               | Ribosomal  | -2,1               | -1,3               |
| TREMBL:Q9C2B9 <i>Neurospora crassa</i> PROBABLE RIBOSOMAL PROTEIN L38.                                   | Ribosomal  | -2,1               | -5,1               |
| SWISSPROT:O60143 <i>Schizosaccharomyces pombe</i> 60S ribosomal protein L7-C.                            | Ribosomal  | -2,1               | -1,6               |
| SWISSPROT:Q10421 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S28 (S33).                       | Ribosomal  | -2,2               | -1,6               |
| TREMBL:Q96UT5 <i>Paracoccidioides brasiliensis</i> PUTATIVE RIBOSOMAL PROTEIN L35.                       | Ribosomal  | -2,2               | -1,5               |
| TREMBL:Q9C3Z6 <i>Podospora anserina</i> RIBOSOMAL PROTEIN P0.  | Ribosomal  | -2,2               | -1,3               |
| SWISSPROT:P36105 <i>Saccharomyces cerevisiae</i> 60S ribosomal protein L14-A.                            | Ribosomal  | -2,2               | -1,5               |
| SWISSPROT:P52810 <i>Podospora anserina</i> 40S ribosomal protein S9 (S7).                                | Ribosomal  | -2,2               | -1,6               |
| TREMBL:Q9URK4 <i>Schizosaccharomyces pombe</i> RIBOSOMAL PROTEIN S16 HOMOLOG (FRAGMENT)                  | Ribosomal  | -2,3               | -1,3               |
| TREMBL:Q9HDQ7 <i>Colletotrichum gloeosporioides</i> PUTATIVE 60S RIBOSOMAL PROTEIN                       | Ribosomal  | -2,3               | -1,9               |
| SWISSPROT:O59953 <i>Neurospora crassa</i> 60S ribosomal protein L5 (CPR4).                               | Ribosomal  | -2,3               | -1,5               |
| TREMBL:CAD37159 <i>Aspergillus fumigatus</i> Putative ribosomal protein.                                 | Ribosomal  | -2,3               | -1,3               |
| SWISSPROT:O14069 <i>Schizosaccharomyces pombe</i> Probable 60S ribosomal protein C1687_06c               | Ribosomal  | -2,4               | -1,3               |
| TREMBL:AAM43909 <i>Aspergillus fumigatus</i> Large subunit ribosomal protein L3                          | Ribosomal  | -2,4               | -1,5               |
| TREMBL:CAA37766 <i>Neurospora crassa</i> Ribosomal protein crp-2   | Ribosomal  | -2,4               | -2,1               |
| SWISSPROT:Q09668 <i>Schizosaccharomyces pombe</i> 60S ribosomal protein L22.                             | Ribosomal  | -2,4               | -2,2               |
| TREMBL:Q96W42 <i>Ophiostoma novo-ulmi</i> RIBOSOMAL PROTEIN L34-LIKE PROTEIN.                            | Ribosomal  | -2,4               | -2,0               |
| SWISSPROT:P27073 <i>Emericella nidulans</i> 40S ribosomal protein S19 (S16).                             | Ribosomal  | -2,4               | -1,9               |
| SWISSPROT:O74892 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S2.                              | Ribosomal  | -2,6               | -1,2               |
| TREMBL:Q9UVN8 <i>Emericella nidulans</i> RIBOSOMAL PROTEIN L16A  | Ribosomal  | -2,7               | -1,5               |
| SWISSPROT:Q10192 <i>Schizosaccharomyces pombe</i> 60S ribosomal protein L18                              | Ribosomal  | -2,7               | -1,4               |
| SWISSPROT:O74893 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S20.                             | Ribosomal  | -2,7               | -1,6               |
| SWISSPROT:Q9C0Z7 <i>Schizosaccharomyces pombe</i> 40S ribosomal protein S6-B.                            | Ribosomal  | -2,7               | -1,4               |
| TREMBL:Q9HFB3 <i>Aspergillus oryzae</i> PACC.  | regulering | 2,4                | 1,3                |
| TREMBL:Q9UVK6 <i>Emericella nidulans</i> MITOGEN-ACTIVATED PROTEIN KINASE.                               | regulering | 2,1                | 1,3                |
| TREMBL:Q9HET3 <i>Aspergillus niger</i> SECRETION RELATED GTPASE (SRGB)                                   | regulering | 1,8                | 2,2                |
| TREMBL:Q9Y899 <i>Emericella nidulans</i> CALCIUM/CALMODULIN DEPENDENT PROTEIN KINASE B.                  | regulering | 1,7                | 1,3                |
| TREMBL:Q9P5Z9 <i>Neurospora crassa</i> RELATED TO NIF-SPECIFIC REGULATORY PROTEIN.                       | regulering | 1,5                | 1,7                |
| SWISSPROT:P36586 <i>Schizosaccharomyces pombe</i> Ras-related protein ypt5.                              | regulering | 1,5                | 1,4                |

| Annotation   | Pathway                      | Fold reg. day 3 | Fold reg. day 4 |
|--|------------------------------|-----------------|-----------------|
| TREMBL:O74251 <i>Emericella nidulans</i> MEDUSA.   | regulering                   | 1,4             | 1,9             |
| SWISSPROT:P87072 <i>Neurospora crassa</i> Calcineurin B subunit (Protein phosphatase 2B regulatory sub                       | regulering                   | 1,4             | 1,9             |
| TREMBL:Q8WZR7 <i>Neurospora crassa</i> PROBABLE GTP-BINDING PROTEIN DRAB11.  | regulering                   | 1,3             | 1,9             |
| TREMBL:Q9C297 <i>Neurospora crassa</i> RAS-2 PROTEIN.  | regulering                   | -1,3            | -1,9            |
| SWISSPROT:Q00771 <i>Emericella nidulans</i> (EC=2.7.1.123) Calcium/calmodulin-dependent protein kinase (EC 2.7.1.123) (      | Regulering                   | -2,2            | -1,3            |
| TREMBL:Q10294 <i>Schizosaccharomyces pombe</i> CAMP-INDEPENDENT REGULATORY PROTEIN PAC2.                                     | Regulering                   | -3,4            | -8,4            |
| GENESEQP:ABP60744 <i>Aspergillus nidulans</i> Aspergillus nidulans thioredoxin SEQ ID NO:93.                                 | redox                        | -1,2            | -2,1            |
| TREMBL:Q9HFR2 <i>Ajellomyces capsulata</i> PUTATIVE THIOL-SPECIFIC ANTIOXIDANT PROTEIN TSA1.                                 | redox                        | -1,3            | -2,3            |
| TREMBL:Q9P5T9 <i>Neurospora crassa</i> PROBABLE NI-BINDING UREASE ACCESSORY PROTEIN (UREG).                                  | purine/pyrimidine metabolism | 1,7             | 1,5             |
| TREMBL:BAC07276 <i>Neurospora crassa</i> (EC=6.3.2.6) 5'-phosphoribosyl-5-aminoimidazole-4-N-succinocarboxamide s            | purine/pyrimidine metabolism | -1,3            | -1,6            |
| TREMBL:Q12610 <i>Emericella nidulans</i> (EC=1.3.1.14) DIHYDROORotate DEHYDROGENASE (EC 1.3.1.14).                           | purine/pyrimidine metabolism | -1,4            | -1,6            |
| TREMBL:CAD37041 <i>Neurospora crassa</i> Nucleoside-diphosphate kinase   | purine/pyrimidine metabolism | -1,7            | -2,2            |
| TREMBL:Q9UTG1 <i>Schizosaccharomyces pombe</i> PUTATIVE PURINE NUCLEOSIDE PHOSPHORYLASE.                                     | purine/pyrimidine metabolism | -2,2            | -1,6            |
| TREMBL:Q8X175 <i>Emericella nidulans</i> KARYOPHERIN ALPHA.  | protein transport nucleus    | -1,4            | -1,4            |
| TREMBL:O93914 <i>Aspergillus niger</i> PDI RELATED PROTEIN A.  | Protein folding              | 2,9             | 5,9             |
| TREMBL:Q9C2N6 <i>Neurospora crassa</i> RELATED TO DNAJ-LIKE PROTEIN HOMOLOG.   | Protein folding              | 1,9             | 1,8             |
| TREMBL:Q9HGM9 <i>Schizosaccharomyces pombe</i> DNAJ DOMAIN PROTEIN SIMILAR TO HUMAN TETRATRICOPEPTIDE REPEA                  | Protein folding              | 1,8             | 1,2             |
| TREMBL:Q8X0V3 <i>Neurospora crassa</i> PROBABLE PEROXISOMAL PROTEIN POX18.   | peroxisom                    | 1,6             | 1,8             |
| TREMBL:Q8WZW4 <i>Neurospora crassa</i> RELATED TO PEROXISOMAL MEMBRANE PROTEIN PMP47B.                                       | peroxisom                    | -1,7            | -2,1            |
| TREMBL:Q59632 <i>Ochrobactrum anthropi</i> (EC=3.4.11.19) D-AMINOPEPTIDASE (EC 3.4.11.19).                                   | peptidase/protease           | 3,2             | 5,1             |
| TREMBL:Q96VC4 <i>Emericella nidulans</i> CARBOXYPEPTIDASE.   | peptidase/protease           | 1,9             | 1,6             |
| TREMBL:Q96VT2 <i>Aspergillus niger</i> (EC=3.4.11.5) PROLYL AMINOPEPTIDASE A (EC 3.4.11.5)                                   | peptidase/protease           | 1,5             | 2,4             |
| TREMBL:Q98L22 <i>Rhizobium loti</i> PROLINE DIPEPTIDASE.   | peptidase/protease           | 1,3             | 2,4             |
| TREMBL:Q9UUR7 <i>Metarhizium anisopliae</i> METALLOPROTEASE MEP1.  | peptidase/protease           | -1,5            | -1,4            |
| TREMBL:AAM55216 <i>Alcaligenes eutrophus</i> 6-chlorhydroxyquinol-1,2-dioxygenase.   | Mitochondriel                | 3,0             | 1,5             |
| SWISSPROT:P14187 <i>Neurospora crassa</i> (EC=4.4.1.17) Cytochrome c heme lyase (EC 4.4.1.17) (CCHL) (Holocytochrome         | Mitochondriel                | 2,2             | 1,3             |
| TREMBL:Q8WZY6 <i>Neurospora crassa</i> PROBABLE COPROPORPHYRINOGEN OXIDASE.  | Mitochondriel                | 1,7             | 1,9             |
| SWISSPROT:P00431 <i>Saccharomyces cerevisiae</i> (EC=1.11.1.5) Cytochrome C peroxidase, mitochondrial precursor (EC 1.11.1.  | Mitochondriel                | 1,4             | 2,3             |
| SWISSPROT:Q07536 <i>Bos taurus</i> (EC=1.2.1.27) Methylmalonate-semialdehyde dehydrogenase [acylating], mitoc                | Mitochondriel                | 1,4             | 1,8             |
| TREMBL:Q9Y857 <i>Kluyveromyces lactis</i> (EC=1.1.2.3) CYTOCHROME B2 PRECURSOR (EC 1.12.3)                                   | Mitochondriel                | 1,4             | 3,7             |
| TREMBL:O74752 <i>Schizosaccharomyces pombe</i> PUTATIVE MITOCHONDRIAL PROTEIN IMPORT PROTEIN.                                | Mitochondriel                | 1,3             | 2,2             |
| SWISSPROT:Q9Y8A7 <i>Emericella nidulans</i> Mitochondrial import inner membrane translocase subunit TIM9                     | Mitochondriel                | -1,2            | -1,8            |
| SWISSPROT:P39515 <i>Saccharomyces cerevisiae</i> Mitochondrial import inner membrane translocase subunit TIM1                | Mitochondriel                | -1,2            | -1,7            |
| SWISSPROT:P38364 <i>Fusarium solani</i> Pisatin demethylase (EC 1.14.--) (Cytochrome P450 57A2).                             | Mitochondriel                | -1,2            | -2,0            |
| SWISSPROT:Q9UUZ9 <i>Aspergillus oryzae</i> Thiazole biosynthetic enzyme, mitochondrial precursor.                            | Mitochondriel                | -1,2            | -2,2            |
| TREMBL:P87230 <i>Schizosaccharomyces pombe</i> PUTATIVE UBIQUINONE BIOSYNTHESIS METHYLTRANSFERASE C4G3.04C                   | Mitochondriel                | -1,3            | -1,4            |
| TREMBL:Q94EK6 <i>Pisum sativum</i> FERRIC-CHELATE REDUCTASE.   | Mitochondriel                | -1,3            | -1,6            |
| TREMBL:Q8WZW6 <i>Neurospora crassa</i> RELATED TO ATP SYNTHASE EPSILON CHAIN (MITOCHONDRIAL).                                | Mitochondriel                | -1,3            | -1,3            |
| SWISSPROT:O74471 <i>Schizosaccharomyces pombe</i> Cytochrome c oxidase polypeptide via mitochondrial precursor               | Mitochondriel                | -1,3            | -2,1            |
| SWISSPROT:Q12233 <i>Saccharomyces cerevisiae</i> (EC=3.6.3.14) ATP synthase G chain, mitochondrial (EC 3.6.3.14)             | Mitochondriel                | -1,3            | -1,9            |
| TREMBL:BAC10043 <i>Oryza sativa</i> Putative cytochrome P450.  | Mitochondriel                | -1,3            | -1,3            |
| SWISSPROT:O13350 <i>Kluyveromyces lactis</i> (EC=3.6.3.14) ATP synthase D chain, mitochondrial (EC 3.6.3.14).                | Mitochondriel                | -1,3            | -1,5            |
| TREMBL:Q9C1X2 <i>Schizosaccharomyces pombe</i> PUTATIVE D-LACTATE DEHYDROGENASE MITOCHONDRIAL                                | Mitochondriel                | -1,4            | -2,6            |
| SWISSPROT:P17505 <i>Saccharomyces cerevisiae</i> (EC=1.1.1.37) Malate dehydrogenase, mitochondrial precursor (EC 1.1.1.37)   | Mitochondriel                | -1,4            | -1,4            |
| SWISSPROT:Q74533 <i>Schizosaccharomyces pombe</i> (EC=1.10.2.2) Probable ubiquinol-cytochrome C reductase complex 14 kDa pro | Mitochondriel                | -1,4            | -1,6            |

| Annotation  | Pathway       | Fold reg. day 3 | Fold reg. day 4 |
|---|---------------|-----------------|-----------------|
| TREMBL:O93980 Aspergillus niger CYTOCHROME C OXIDASE SUBUNIT V.   | Mitochondrial | -1,4            | -2,3            |
| SWISSPROT:P00427 <i>Saccharomyces cerevisiae</i> (EC=1.9.3.1) Cytochrome c oxidase polypeptide VI, mitochondrial precursor  | Mitochondrial | -1,5            | -1,6            |
| TREMBL:Q8WZW8 <i>Neurospora crassa</i> PROBABLE YHM1 (MITOCHONDRIAL CARRIER).   | Mitochondrial | -1,5            | -1,2            |
| SWISSPROT:P40086 <i>Saccharomyces cerevisiae</i> Cytochrome c oxidase assembly protein COX15.                               | Mitochondrial | -1,6            | -1,5            |
| TREMBL:Q9P5U4 <i>Neurospora crassa</i> GRPE PROTEIN HOMOLOG.  | Mitochondrial | -1,6            | -2,5            |
| SWISSPROT:P37211 <i>Neurospora crassa</i> (EC=3.6.3.14) ATP synthase alpha chain, mitochondrial precursor (EC 3.6.3.        | Mitochondrial | -1,6            | -1,3            |
| SWISSPROT:P09940 <i>Pichia jadinii</i> ATPase inhibitor, mitochondrial.   | Mitochondrial | -1,7            | -2,2            |
| SWISSPROT:Q92328 <i>Saccharomyces cerevisiae</i> Mitochondrial inheritance component MDM12.                                 | Mitochondrial | -1,7            | -1,3            |
| SWISSPROT:P81449 <i>Saccharomyces cerevisiae</i> (EC=3.6.3.14) ATP synthase e chain, mitochondrial (EC 3.6.3.14).           | Mitochondrial | -1,7            | -1,3            |
| TREMBL:Q94284 <i>Schizosaccharomyces pombe</i> SULFIDE:QUINONE OXIDOREDUCTASE PRECURSOR (EC 1.1.1.1).                       | Mitochondrial | -1,8            | -2,5            |
| SWISSPROT:P56525 <i>Neurospora crassa</i> (EC=3.6.3.14) ATP synthase delta chain, mitochondrial precursor (EC 3.6.3.        | Mitochondrial | -1,8            | -1,7            |
| SWISSPROT:P56205 <i>Aspergillus niger</i> Cytochrome c.   | Mitochondrial | -1,8            | -3,1            |
| SWISSPROT:P02723 <i>Neurospora crassa</i> ADP,ATP carrier protein (ADP/ATP translocase) (Adenine nucle                      | Mitochondrial | -1,8            | -1,5            |
| TREMBL:O94705 <i>Schizosaccharomyces pombe</i> (EC=1.9.3.1) PUTATIVE CYTOCHROME C OXIDASE POLYPEPTIDE C1259_05C (EC 1.9.    | Mitochondrial | -2,1            | -2,7            |
| ERDBP:NP000634 <i>Aspergillus oruzae</i> Deduced amino acid sequence for <i>A. oryzae</i> EST AO365 having hi               | metabolism    | 3,0             | 4,8             |
| ERDBP:NP000634 <i>Aspergillus oruzae</i> Deduced amino acid sequence for <i>A. oryzae</i> EST AO365 having hi               | metabolism    | 2,8             | 4,8             |
| TREMBL:Q97DL0 <i>Clostridium acetobutylicum</i> AMIDASE FROM NICOTINAMIDASE FAMILY.   | metabolism    | 2,6             | 11,4            |
| TREMBL:P87017 <i>Aspergillus parasiticus</i> SHORT-CHAIN ALCOHOL DEHYDROGENASE.   | metabolism    | 2,3             | 2,1             |
| SWISSPROT:P07547 <i>Emericella nidulans</i> (EC=2.5.1.19) Pentafunctional AROM polypeptide [Includes: 3-dehydroquinate      | metabolism    | 2,2             | 3,5             |
| TREMBL:AAM43715 <i>Dictyostelium discoideum</i> Putative Guanine-nucleotide releasing factor.                               | metabolism    | 2,1             | 2,3             |
| TREMBL:Q9HEE3 <i>Neurospora crassa</i> RELATED TO SORBITOL UTILIZATION PROTEIN SOU1.  | metabolism    | 2,0             | 3,8             |
| TREMBL:Q96V04 <i>Magnaporthe grisea</i> ACETOLACTATE SYNTHASE SMALL-SUBUNIT-LIKE PROTEIN.                                   | metabolism    | 2,0             | 1,2             |
| TREMBL:Q8X1W7 <i>Monascus anka</i> ACID PHOSPHATASE.  | metabolism    | 2,0             | 1,5             |
| TREMBL:Q9X91 Streptomyces coelicolor PUTATIVE ZINC-BINDING DEHYDROGENASE.   | metabolism    | 1,7             | 1,6             |
| SWISSPROT:P16928 <i>Emericella nidulans</i> (EC=6.2.1.1) Acetyl-coenzyme A synthetase (EC 6.2.1.1) (Acetate-CoA lig.        | metabolism    | 1,7             | 1,7             |
| SWISSPROT:Q01278 <i>Neurospora crassa</i> (EC=3.6.3.14) Vacuolar ATP synthase subunit E (EC 3.6.3.14) (V-ATPase E su        | metabolism    | 1,6             | 1,2             |
| ERDBP:NP000805 <i>Aspergillus niger</i> hemA (5-aminolevulinate synthase) gene of <i>Aspergillus nige</i>                   | metabolism    | 1,5             | 1,3             |
| TREMBL:Q9P3R9 <i>Neurospora crassa</i> PROBABLE NICOTINATE-NUCLEOTIDE PYROPHORYLASE (CARBOXYLAT                             | metabolism    | 1,5             | 1,4             |
| TREMBL:O14344 <i>Schizosaccharomyces pombe</i> (EC=1.1.1.205) PROBABLE INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE (EC 1.1.1.20  | metabolism    | 1,5             | 3,8             |
| SWISSPROT:Q09751 <i>Schizosaccharomyces pombe</i> (EC=4.4.1.5) Probable lactoylglutathione lyase (EC 4.4.1.5) (Methylglyoxa | metabolism    | 1,5             | 1,3             |
| TREMBL:Q74624 <i>Trichoderma reesei</i> (EC=2.7.7.13) MANNOSE-1-PHOSPHATE GUANYLTRANSFERASE (EC 2.7.7.13) (MPG1 TR          | metabolism    | 1,5             | 1,5             |
| GENESEQP:AAV18136 <i>Thielavia terrestris</i> T. terrestris uroporphyrinogen decarboxylase protein sequenc                  | metabolism    | 1,4             | 1,4             |
| GENESEQP:AAM00105 <i>Physcomitrella patens</i> Triosephosphate transporter sequence #173.                                   | metabolism    | 1,4             | 2,8             |
| TREMBL:Q12707 <i>Sporobolomyces salmonicolor</i> (EC=1.1.1.2) NADPH-DEPENDENT ALDEHYDE REDUCTASE (EC 1.1.1.2)               | metabolism    | 1,4             | 1,2             |
| SWISSPROT:Q12657 <i>Penicillium chrysogenum</i> (EC=2.7.1.25) Adenylylsulfate kinase (EC 2.7.1.25) (APS kinase) (Adenosine  | metabolism    | 1,3             | 1,7             |
| TREMBL:Q9Y7D1 <i>Aspergillus terreus</i> TRANSESTERASE  | metabolism    | -1,2            | -3,4            |
| TREMBL:Q9AGP8 <i>Arthrobacter globiformis</i> N,N-DIMETHYLYGLYCINE OXIDASE  | metabolism    | -1,5            | -1,7            |
| TREMBL:Q9Z4Y6 <i>Streptomyces coelicolor</i> PUTATIVE SALICYLATE HYDROXYLASE  | metabolism    | -1,7            | -1,9            |
| TREMBL:Q96WL1 <i>Aspergillus parasiticus</i> AFLATOXIN EFFLUX PUMP AFLT   | metabolism    | -1,7            | -1,4            |
| SWISSPROT:P42882 <i>Aspergillus parasiticus</i> NMT1 protein homolog  | metabolism    | -1,9            | -4,5            |
| TREMBL:Q9FC45 <i>Streptomyces coelicolor</i> PUTATIVE INTEGRAL MEMBRANE PROTEIN.  | membrane      | 2,2             | 4,3             |
| TREMBL:Q9P5Y3 <i>Neurospora crassa</i> RELATED TO SYNTAXIN 8.   | membrane      | 1,8             | 1,9             |
| TREMBL:Q8X090 <i>Neurospora crassa</i> RELATED TO SYNTAXIN 12.  | membrane      | 1,8             | 1,6             |
| TREMBL:O13312 <i>Aspergillus parasiticus</i> SYNAPTOBREVIN  | membrane      | 1,5             | 1,7             |
| TREMBL:Q9P864 <i>Pichia jadinii</i> PUTATIVE MEMBRANE PROTEIN.  | membrane      | 1,5             | 1,7             |
| TREMBL:Q8X175 <i>Emericella nidulans</i> KARYOPHERIN ALPHA.   | membrane      | 1,4             | 1,3             |
| TREMBL:O13657 <i>Schizosaccharomyces pombe</i> PROBABLE MEMBRANE PROTEIN YOL130W  | membrane      | 1,4             | 1,5             |

| Annotation  | Pathway             | Fold reg day 3 | Fold reg day 4 |
|---|---------------------|----------------|----------------|
| TREMBL:Q9UX8 Neurospora crassa P-TYPE ATPASE (FRAGMENT).  | Ion-transport       | 1,9            | 2,5            |
| TREMBL:Q9HE83 Neurospora crassa PROBABLE PHOSPHATE TRANSPORT PROTEIN MIR1.  | Ion-transport       | -1,3           | -2,5           |
| TREMBL:Q96TH7 Aspergillus fumigatus PLASMA MEMBRANE H+-ATPASE   | Ion-transport       | -1,4           | -1,6           |
| TREMBL:O59940 Neurospora crassa CALCIUM/PROTON EXCHANGER.   | Ion-transport       | -1,4           | -4,0           |
| SWISSPROT:Q13733 Homo sapiens (EC=3.6.3.9) Sodium/potassium-transporting ATPase alpha-4 chain (EC 3.6.3)              | Ion-transport       | -1,5           | -1,8           |
| TREMBL:Q38998 Arabidopsis thaliana AKT1 POTASSIUM TRANPORTER.   | Ion-transport       | -1,6           | -1,3           |
| TREMBL:Q9HE83 Neurospora crassa PROBABLE PHOSPHATE TRANSPORT PROTEIN MIR1.  | Ion-transport       | -1,8           | -2,4           |
| TREMBL:Q9P426 Ajellomyces capsulata N-GLYCOSYL-TRANSFERASE.   | Glycosylering Golgi | 1,9            | 2,0            |
| TREMBL:Q96VV1 Aspergillus awamori PROTEIN O-MANNOSYL TRANSFERASE.   | Glycosylering       | 1,8            | 1,7            |
| GENESEQP:AAR47201 Saccharomyces cerevisiae DPM2 mannosyl transferase.   | Glycosylering       | -1,9           | -2,0           |
| TREMBL:AAL82734 Aspergillus fumigatus Structural maintenance of chromosome protein.                                   | DNA                 | 2,2            | 2,4            |
| TREMBL:O14147 Schizosaccharomyces pombe HYPOTHETICAL 96.2 kDa HELICASE C3G6.11 IN CHROMOSOME !                        | DNA                 | 1,6            | 2,4            |
| SWISSPROT:Q9P605 Schizosaccharomyces pombe (EC=3.6.1.23) Probable deoxyuridine 5'-triphosphate nucleotidohydrolase/EC | DNA                 | 1,5            | 1,6            |
| TREMBL:Q8X0K1 Neurospora crassa RELATED TO POL12 (DNA-DIRECTED DNA POLYMERASE ALPHA).                                 | DNA                 | 1,5            | 1,5            |
| TREMBL:O94395 Schizosaccharomyces pombe PUTATIVE ATP-DEPENDENT DNA HELICASE.  | DNA                 | 1,4            | 1,8            |
| SWISSPROT:Q09176 Schizosaccharomyces pombe Splicing factor U2AF 23 kDa subunit (U2 auxiliary factor 23                | DNA                 | 1,4            | 1,5            |
| SWISSPROT:P48003 Schizosaccharomyces pombe Histone H2A variant.   | DNA                 | 1,4            | 1,2            |
| TREMBL:Q9P3G2 Neurospora crassa (EC=1.17.4.1) RIBONUCLEOSIDE-DIPHOSPHATE REDUCTASE LARGE CHAIN (EC 1.17.4.            | DNA                 | 1,3            | 2,3            |
| TREMBL:CAD37005 Neurospora crassa Related to mismatched base pair and cruciform dna recognition                       | DNA                 | -2,0           | -8,9           |
| SWISSPROT:O75001 Schizosaccharomyces pombe DNA replication licensing factor mcm7 (Minichromosome mainte               | DNA                 | -2,6           | -1,9           |
| GENESEQP:AAU00959 Fusarium venenatum F. venenatum glucanase polypeptide.  | Cell-wall           | 5,9            | 4,6            |
| TREMBL:Q9P8U4 Aspergillus fumigatus BETA (1-3) GLUCANOSYLTRANSFERASE GEL2P.   | Cell-wall           | 2,2            | 2,7            |
| SWISSPROT:Q09196 Schizosaccharomyces pombe Myosin regulatory light chain cdc4.  | cell-wall           | 1,9            | 1,9            |
| TREMBL:Q9HFQ2 Emericella nidulans (EC=3.1.3.16) PROTEIN PHOSPHATASE 2A.   | Cell-wall           | 1,9            | 1,5            |
| TREMBL:Q96UK5 Coccidioides immitis BETA-GLUCOSIDASE 5 (FRAGMENT).   | Cell-wall           | 1,9            | 1,3            |
| TREMBL:Q9P8U4 Aspergillus fumigatus BETA (1-3) GLUCANOSYLTRANSFERASE GEL2P.   | Cell-wall           | 1,8            | 2,2            |
| TREMBL:Q52423 Pseudomonas sp. ENDO ALPHA-1,4 POLYGALACTOSAMINIDASE PRECUSOR PRECURSOR.                                | Cell-wall           | 1,7            | 3,8            |
| TREMBL:O74687 Aspergillus fumigatus GEL1 PROTEIN.   | Cell-wall           | 1,7            | 1,6            |
| TREMBL:Q8WZQ2 Neurospora crassa RELATED TO CEL1 PROTEIN.  | Cell-wall           | 1,7            | 24,2           |
| SWISSPROT:P40414 Saccharomyces cerevisiae Tropomyosin 2.  | cell-wall           | 1,7            | 1,3            |
| TREMBL:Q92225 Emericella nidulans 1,3-BETA-D-GLUCAN SYNTHASE CATALYTIC SUBUNIT.                                       | Cell-wall           | 1,7            | 1,2            |
| TREMBL:Q9C1M3 Emericella nidulans SEPTIN.   | cell-wall           | 1,5            | 2,3            |
| TREMBL:Q9C1M3 Emericella nidulans SEPTIN.   | cell-wall           | 1,5            | 1,6            |
| SWISSPROT:Q10133 Schizosaccharomyces pombe Rho2 protein.  | Cell-Wall           | 1,5            | 2,1            |
| TREMBL:Q9UR09 Schizosaccharomyces pombe CELL WALL SYNTHESIS PROTEIN PSU1  | cell-wall           | 1,5            | 2,0            |
| TREMBL:AAN00330 Streptococcus agalactiae Cell wall surface anchor family protein                                      | cell-wall           | 1,4            | 1,6            |
| TREMBL:Q9P7E8 Schizosaccharomyces pombe ACTIN BINDING PROTEIN WITH SH3 DOMAINS.                                       | Cell-Wall           | 1,4            | 1,6            |
| TREMBL:Q9C1M2 Emericella nidulans SEPTIN.   | cell-wall           | 1,4            | 1,5            |
| TREMBL:Q96VD0 Xanthoria parietina HYDROPHOBIN H1 PRECURSOR.   | cell-wall           | 1,3            | 1,5            |
| TREMBL:Q9C3Y4 Emericella nidulans RHO GTPASE.   | Cell-Wall           | 1,3            | 1,5            |
| TREMBL:Q9P302 Emericella nidulans HYPERCELLULAR PROTEIN.  | Cell-Wall           | -1,4           | -1,3           |
| TREMBL:Q9C1L5 Neurospora crassa PUTATIVE RHO GDP DISSOCIATION INHIBITOR G6G8.3  | Cell-Wall           | -1,4           | -1,3           |
| TREMBL:CAD22154 Volvox carteri Pherophorin-dz1 protein.   | Cell-Wall           | -1,7           | -4,6           |
| TREMBL:Q9P8U3 Aspergillus fumigatus BETA (1-3) GLUCANOSYLTRANSFERASE GEL3P (FRAGMENT).                                | Cell-Wall           | -1,9           | -2,1           |
| TREMBL:Q07229 Saccharomyces cerevisiae VERPROLIN.   | Cell-Wall           | -1,9           | -31,4          |
| TREMBL:Q9P3F4 Neurospora crassa RELATED TO CHITINASE 3 PRECURSOR PROTEIN.   | Cell-Wall           | -2,2           | -2,6           |
| SWISSPROT:Q04951 Saccharomyces cerevisiae Probable family 17 glucosidase SCW10 precursor (EC 3.2.1.-)                 | Cell-Wall           | -2,3           | 1,5            |
| TREMBL:AAC49609 Saccharomyces diastaticus Glucoamylase.   | Carbon-metabolism   | 2,5            | 1,2            |
| TREMBL:Q96WT4 Aspergillus oryzae MALTASE  | Carbon-metabolism   | 2,3            | 5,9            |
| GENESEQP:AAW88044 Acremonium sp. An enzyme with sugar transferase activity  | Carbon-metabolism   | 1,9            | 2,3            |

| Annotation  | Pathway           | Fold reg. day 3 | Fold reg. day 4 |
|---|-------------------|-----------------|-----------------|
| GENESEQP:AAY56815 <i>Bacillus</i> sp. <i>Bacillus</i> D-arabinitol dehydrogenase.   | Carbon-metabolism | 1,9             | 1,4             |
| TREMBL:Q9P8R5 <i>Aspergillus niger</i> D-XYLOSE REDUCTASE.  | Carbon-metabolism | 1,6             | 1,6             |
| TREMBL:AAM46059 <i>Oryza sativa</i> Putative aldose 1-epimerase-like protein.   | Carbon-metabolism | 1,6             | 3,5             |
| SWISSPROT:P50166 <i>Candida tropicalis</i> (EC=1.1.1.250) D-arabinitol 2-dehydrogenase [ribulose forming] (EC 1.1.1.25)   | Carbon-metabolism | 1,6             | 2,5             |
| TREMBL:Q9TEM3 <i>Emericella nidulans</i> (EC=4.1.3.31) METHYLCITRATE SYNTHASE PRECURSOR (EC 4.1.3.31).                    | Carbon-metabolism | 1,6             | 1,4             |
| TREMBL:Q9URW9 <i>Schizosaccharomyces pombe</i> PROBABLE ALDEHYDE DEHYDROGENASE.   | Carbon-metabolism | 1,5             | 1,2             |
| SWISSPROT:P44538 <i>Haemophilus influenzae</i> (EC=3.5.99.6) Glucosamine-6-phosphate isomerase (EC 3.5.99.6) (Glucosamine | Carbon-metabolism | 1,4             | 3,1             |
| TREMBL:CAD36981 <i>Neurospora crassa</i> Related to glucosidase II, alpha subunit.  | Carbon-metabolism | 1,4             | 1,8             |
| TREMBL:Q9HGZ3 <i>Aspergillus oryzae</i> HEXOKINASE.   | Carbon-metabolism | 1,4             | 1,5             |
| GENESEQP:AAR70209 <i>Aspergillus niger</i> A. niger alpha-galactosidase.  | Carbon-metabolism | 1,3             | 3,1             |
| TREMBL:Q9P8D6 <i>Aspergillus niger</i> (EC=4.1.3.7) CITRATE SYNTHASE PRECURSOR (EC 4.1.3.7)                               | Carbon-metabolism | -1,2            | -1,9            |
| TREMBL:Q9HGY8 <i>Aspergillus oryzae</i> (EC=5.3.1.1) TRIOSEPHOSPHATE ISOMERASE (EC 5.3.1.1) (TIM).                        | Carbon-metabolism | -1,3            | -2,8            |
| TREMBL:Q9HGY7 <i>Aspergillus oryzae</i> GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE.   | Carbon-metabolism | -1,3            | -1,8            |
| SWISSPROT Q12560 <i>Aspergillus oryzae</i> (EC=4.2.1.11) Enolase (EC 4.2.1.11) (2-phosphoglycerate dehydratase) (2-ph     | Carbon-metabolism | -1,4            | -1,4            |
| TREMBL:Q9C415 <i>Aspergillus oryzae</i> (EC=1.2.1.12) GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE (EC 1.2.1.12).             | Carbon-metabolism | -1,4            | -2,1            |
| SWISSPROT:O13309 <i>Pichia stipitis</i> (EC=1.1.1.1) Alcohol dehydrogenase II (EC 1.1.1.1) (ADH 1).                       | Carbon-metabolism | -1,4            | -1,5            |
| TREMBL:Q9C253 <i>Neurospora crassa</i> PROBABLE GLYCERONE KINASE ISOFORM.   | Carbon-metabolism | -1,5            | -1,3            |
| TREMBL:Q9P8D6 <i>Aspergillus niger</i> (EC=4.1.3.7) CITRATE SYNTHASE PRECURSOR (EC 4.1.3.7).                              | Carbon-metabolism | -1,7            | -2,8            |
| TREMBL:Q9HE50 <i>Neurospora crassa</i> RELATED TO MALATE DEHYDROGENASE (OXALOACETATE-DECARBOXYLATION).                    | Carbon-metabolism | -1,8            | -1,6            |
| TREMBL:Q94185 <i>Aspergillus oryzae</i> PYRUVATE DECARBOXYLASE.   | Carbon-metabolism | -2,2            | -7,3            |
| ERDBP:NP000614 <i>Aspergillus oryzae</i> Deduced amino acid sequence for A.oryzae EST AS1789 having h                     | AO EST            | 1,6             | 1,4             |
| ERDBP:NP000292 <i>Aspergillus oryzae</i> Deduced amino acid sequence of genomic DNA sequence encoding                     | AO EST            | -2,3            | -3,8            |